REMARKS

The Examiner provides a number of rejections and we list them here in the order in which they are addressed:

I. Claims 1, 6-8, 10-13, and 15-19 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Mikkelsen et al., Nucleic Acids Research, 20:2249-2255 (1992).

II. Obviousness (35 U.S.C. § 103(a)

A. Claims 1-5, 29, and 32-35 are rejected as allegedly being unpatentable over US Patent No. 5,8800,327 To Lubon et al. (Lubon I), in view of Mikkelsen et al.

B. Claims 1, 16-18, and 20-28 are rejected as allegedly being unpatentable over Lubon I, in view of Mikkelsen et al., in further view of Coppes et al., Radiation Research, 153:339-346 (2000).

C. Claims 29, and 32-35 are rejected as allegedly being unpatentable over Mikkelsen et al. in view of Lubon I.

D. Claims 41-47 are rejected as allegedly being unpatentable over Mikkelsen et al. in view of US Patent No. 5,965,789 To Lubon et al (Lubon II).

E. Claims 48-50 are rejected as allegedly being unpatentable over Mikkelsen et al., in view of Lubon II, in further view of Coppes et al.

III. Claims 1-13, 15-29,32-35, and 41-50 are rejected under 35 USC §112, ¶1 as allegedly failing to comply with the enablement requirement.

I. Claims 1, 6-8, 10-13, and 15-19 Are Not Anticipated by Mikkelsen et al.

As the Examiner is well aware, a single reference must disclose each limitation of a claim in order for that reference to anticipate the claim. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). This criterion is not met with the Mikkelsen et al. reference.

The Examiner suggests that Mikkelsen et al. discloses each and every element encompassed by the Applicant's claimed invention:

> Mikkelsen teaches transgenic mouse ... [comprising] ... an exogenous nucleic acid [encoding human blood coagulation factor VIII-C terminal peptide] ... operably linked to a salivary gland transcription control region ... the polypeptide is secreted in samples of collective saliva ... (about 0.05 ml of saliva) of about 10 units ...

Office Action pg. 10. The Applicant disagrees because the Examiner has provided an admission that:

> Mikkelson differs from the claimed invention by not teaching salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of a transgenic cow.

Office Action pp. 14, 15, & 16. Further, the Examiner is not considering the Applicant's claim element regarding the secretion of an exogenous protein at a concentration of approximately 0.5 mg/ml. The Examiner is reminded that Mikkelsen et al. defines "a unit":

> One unit equals the ELISA measurement of FVIII antigen present in 1 ml of normal human plasma.

Mikkelsen et al., Figure 7 Legend, pg. 2253. The Examiner has not fulfilled the burden of evidence to demonstrate that 10 units of FVIII activity corresponds to 0.5 mg/ml of protein.[1] Mikkelsen et al. certainly contains no such teaching and, as such, can not anticipate the presently claimed invention.

The Applicant, therefore, respectfully requests that the Examiner withdraw the present rejection.

[1] Lubon I teaches that 0.5 mg of Factor VIII corresponds to 2,500 units. *col 2 ln 45-46.*

II. The Claims Are Not *Prima Facie* Obvious

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP § 2142*; Establishing A *Prima Facie* Case Of Obviousness. The Examiner is reminded that if ONLY ONE of the above requirements is not met, then a prima facie case of obviousness does not exist. The Applicant submits that the Examiner's rejection does not meet these criteria. The Applicant rebuts the establishment of a *prima facie* case of obviousness by the argument below.

A. Claims 1-5, 29, And 32-35 Are Not Obvious Over Lubon I & Mikkelsen et al.

1. There Is No Motivation In Lubon I For Combination With Mikkelsen's Teachings

The Examiner rejects the Applicant's presently claimed embodiments directed to collecting exogenous proteins from saliva by stating that:

> Lubon offers motivation for using mammals producing large volumes of body fluids in stating that an important need remains for an efficient and relatively inexpensive means of producing large quantities of infectious-free, human F8 protein suitable for clinical use (column 2, lines 35-37).

Office Action pg 11. The Applicant disagrees. Specifically, Lubon I does not mention saliva. Lubon I only offers milk and urine as possible sources of secreted proteins. Mikkelsen et al. does not discuss any options for the secretion of exogenous proteins into either milk or urine. Consequently, one having ordinary skill in the art would not find Lubon I providing any motivation to seek and consider the teachings of Mikkelsen et al. The Examiner has not provided any evidence to the contrary.

The Examiner has the burden of showing that the combination of the cited art is justified by "evidence" which supplies a suggestion, teaching or motivation sufficient to provide one skilled in the art to create the Applicant's invention. This requirement is "an essential evidentiary component of an obviousness holding." *C.R. Bard, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998). There are three sources for this evidentiary component: the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). The suggestion most often comes from the teachings of the pertinent

references. *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998). Nonetheless, regardless of the source of the requisite evidence, the Examiner's showing "must be clear and particular, and broad conclusory statements about the teaching of [a]... reference[], standing alone, are not 'evidence'." *In re Dembiczak,* 175 F.3d 994, 1000 (Fed. Cir. 1999).

Consequently, Lubon I and Mikkelsen et al. are improperly combined. The Applicant respectfully requests the Examiner to withdraw the present rejection.

2. Lubon I And Mikkelsen et al. Do Not Teach All The Claimed Elements

Even if the references were properly combined (which they are not) a *prima facie* case of obviousness still fails because the two references fail to teach all the claimed elements. In particular, neither reference teaches secreting an exogenous protein at a concentration of at least 0.5 mg/ml. The Applicant respectfully requests the Examiner to withdraw the present rejection.

3. Lubon I and Mikkelsen et al. Do Not Provide Any Reasonable Expectation Of Success

Because both Lubon I and Mikkelsen et al. fail to disclose the secretion of any protein at a concentration of at least 0.5 mg/ml, neither reference can possibly provide any reasonable expectation of success to achieve this expression level. The Examiner is reminded that a cited reference must explicitly predict that that the claimed embodiment will work:

> The expectation of success must come from the prior art and explicitly predict that the process recited in the claims would work.

In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). Further, the Examiner states that:

> Since the mouse of Mikkelsen contains a construct indistinguishable from the claimed cows, goats, sheep, and pigs or horses of claims 2-5, the mammals of claims 2-[5] would reasonably be expected to produce FVIII at the same levels as Mikkelsen's mice.

Office Action, pg. 11. The Examiner provides here an implication that production of exogenous proteins in transgenic animals (regardless of species, exogenous protein, and expression level) is predictable. This argument is completely contrary to that presented elsewhere in the Office Action concluding that the production of exogenous proteins in transgenic animals is unpredictable:

> This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to

> direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys. 1996, 58: 209-229), for example on page 217, which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene). Also Samuelson provided an extensive review of the limitations of known salivary gland promoters.

Office Action, pg. 4. The Applicant believes that such contradictions only further provides evidence that the Examiner has not provided a *prima facie* case of obviousness regarding a reasonable expectation of success. The Examiner's arguments are undermined by simultaneously asserting contradictory legal and scientific argument.

The Applicant respectfully requests the Examiner to withdraw the present rejection.

B. Claims 1, 16-18, and 20-28 Are Not Obvious Over Lubon I, Mikkelsen et al., and Coppes et al.

The Applicant has shown above that Lubon I & Mikkelsen et al. represents an improper combination and do not provide a proper basis for a *prima facie* case of obviousness. Several deficiencies exist, most notably, neither reference teach the secretion of an exogenous protein into saliva by a transgenic animal at a level of approximately 0.5 mg/ml. In order for Coppes et al. to have merit in a further combination, Coppes et al. must fill this deficiency. Coppes et al. does not.

The Examiner relies upon Coppes et al. because:

> Coppes teaches the insertion of a duct cannula made from Medical Grade Silicone Tubing inserted into the parotid glands of rats aft a small incision (p 340).

Office Action pg. 13. Coppes et al. has no teaching related to the expression of exogenous proteins in transgenic animals and does not alter the above analysis regarding Lubon I and Mikkelsen et al. This deficiency results in Coppes et al. being non-analogous art.

Consequently, the Applicant respectfully requests that the Examiner withdraw the present rejection.

C. Claims 29, and 32-35 Are Not Obvious over Mikkelsen et al. & Lubon I.

1. There Is No Motivation In Mikkelsen et al. For Combination With Lubon I's Teachings

The Examiner has admitted to the very issues that demonstrate that a *prima facie* case of obviousness does not exist for this reference combination. Mikkelsen et al. and Lubon I are improperly combined because the references do not teach transgenic technology using the same species or using the same secreted fluid:

> Mikkelsen teaches transgenic mouse whose genome comprises an exogenous nucleic acid encoding the human blood coagulation factor VIII-C ... secreted in the saliva.

Office Action, pg. 13, and

> Lubon teaches the production of transgenic ... cows, goats, sheep, and pigs expressing ... Factor VIII ... in milk.

Office Action pg. 14. The Examiner has admitted that the Applicant's technology is unpredictable, especially when dealing with salivary PSP promoters (*supra*). Consequently, the Examiner has no basis for the following conclusion:

> Since the mouse of Mikkelsen contains a construct indistinguishable from the claimed cows, the mammals of claims 32-35 would reasonably be expected to produce FVIII at the same levels as Mikkelsen's mice.

Office Action pg 14. This represents a conclusory statement by the Examiner that has no authoritative basis found in the cited references.

The Examiner has further admitted that:

> Mikkelsen differs from the claimed invention by not teaching salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of a transgenic cow.

Office Action pg 14. Lubon I does not fill this admitted deficiency.

The Applicant respectfully requests that the Examiner withdraw the present rejection.

D. Claims 41-47 Are Not Obvious Over Mikkelsen et al. & Lubon II.

1. There Is No Motivation In Mikkelsen et al. For Combination With Lubon II's Teachings

The Examiner relies upon the following to allegedly establish Lubon II as a properly cited reference for this obviousness rejection:

> Lubon teaches a mouse expressing human prothrombin and F8 under the control of the WAP, promoter where the mouse produced detectable quantities [of] prothrombin in its saliva (column 5, lines 13-18).

Office Action pg. 15. This statement is incorrect. Nothing in Lubon II even remotely suggests that prothrombin was successfully secreted into saliva, much less at "detectable quantities". Lubon II barely mentions saliva as a potential bodily fluid, and never develops any discussion or

provides any examples related to making and using a transgenic animal capable of producing exogenous proteins in saliva. Such a disclosure has been determined by the Federal Circuit as only 'obvious to try' and does not provide a proper basis for an obviousness rejection. The Examiner is reminded that 'obvious to try' and 'obviousness' are not equivalent and is well settled patent law:

> An invention is not obvious where the prior art gives 'no direction as to which of many possible choices is likely to be successful.

Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 166 F. Supp.2d 19, 36 (D. N.J. 2001), aff'd, 320 F.3d 1339, 65 USPQ2d 1961 (Fed. Cir. 2003); and

> A finding ... that the patented invention may have been 'obvious to try' from the prior art will not invalidate it. Prior art that makes the invention only 'obvious to try' rather than 'obvious' 'gives either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful'.

Bristol-Meyers Squibb Co. v. Ben Venue Laboratories, Inc., 246 F.3d 1368, 58 USPQ2d 1508 (Fed. Cir. 2001). Even the Examples provided by Lubon II are not related to prothrombin secretion. Lubon II's Examples describe the secretion of Human Protein C in milk, not saliva.

The Applicant respectfully requests the Examiner to withdraw the present rejection.

2. Mikkelsen et al. And Lubon II Do Not Teach All The Claimed Elements

The Examiner has admitted that:

> Mikkelsen differs from the claimed invention by not teaching salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of a transgenic cow.

Office Action pg 15 & 16. Lubon II does not fill this admitted deficiency. In fact, the Examiner admits that Lubon II cannot produce a protein meeting all the Applicant's claimed elements:

> Lubon teaches a mouse expressing human prothrombin ... [having] ... detectable quantities ... in its saliva.

Office Action pg. 15. Again, the Examiner is incorrect in arguing that Lubon II teaches the secretion of "detectable quantities" of a protein into saliva. No such teaching is present. Nevertheless, the Examiner is reminded that Claim 41 recites that the secreted protein has a level

of "at least 0.5 mg/ml", to which (at best) "detectable quantities" is an insufficient disclosure. As argued above, Mikkelsen et al. only teaches protein production in saliva at a level of 10 units (which would appear to translate to approximately 0.002 mg).

Consequently, neither Mikkelsen et al. nor Lubon II teach the expression of an exogenous protein into saliva at a concentration of at least 0.5 mg/ml. The Applicant respectfully requests the Examiner to withdraw the present rejection.

E. Claims 48-50 Are Not Obvious Over Mikkelsen et al., Lubon II, and Coppes et al.

The Applicant has shown above that Mikkelsen et al. & Lubon II represents an improper combination and do not provide a proper basis for a *prima facie* case of obviousness. Several deficiencies exist, most notably, neither reference teach the production of an exogenous protein in a transgenic animal at a concentration of approximately 0.5 mg/ml. In order for Coppes et al. to have merit in a further combination, Coppes et al. must fill this deficiency. Coppes et al. does not.

The Examiner relies upon Coppes et al. because:

> Coppes teaches the insertion of a duct cannula made from Medical Grade Silicone Tubing inserted into the parotid glands of rats aft a small incision (p 340).

Office Action pg. 16. Coppes et al. has no teaching related to the expression of exogenous proteins in transgenic animals and does not alter the above analysis regarding Mikkelsen et al. and Lubon II

Consequently, the Applicant respectfully requests that the Examiner withdraw the present rejection.

III. Claims 1-13, 15-29, 32-35, and 41-50 Are Enabled

The Examiner rejects Claims 1-13, 15-29, 32-35, and 41-50 because:

> ... the specification ... does not reasonably provide enablement for a transgenic non-human mammal ...

Office Action pg. 3. The Examiner maintains that the specification teaches that "salivary gland and saliva specific regulatory elements are necessary to achieve saliva specific expression of a polypeptide of interest." The Examiner, however, believes that the specification "does not disclose which saliva regulatory elements could be used to create any of the transgenic mammals

embraced by the claims". *Office Action pg. 3.* The Applicant disagrees and presents arguments below consistent with the three issues outlined by the Examiner.

A. Salivary Protein Expression Is Not Promoter Specific

The Examiner is requested to review the attached publication abstracts showing the state of the art at the time the present invention was filed. In these publications, it is clear that salivary-specific promoters are not required for successful protein secretion from a salivary gland. For instance, secretion of exogenous protein from salivary gland was achieved using a cytomegalovirus promoter:

> A single injection of Ad.CMV-cHK at a does of 4 x 10(9) pfu resulted in a sustained expression of human tissue kallikrein in rat salivary glands.

Wang et al., "Expression of human tissue kallikrein in rat salivary glands and its secretion into circulation following adenovirus-mediated gene transfer", *Immunopharm* 36:221-227 (1997). Further, high level exogenous protein expression using a PSP promoter was reported to be a reliable technique:

> ... a 25 kb cosmid-derived DNA fragment (PspX25) carrying the structural gene and large flanking areas of Psp is expressed in all 14 analysed lines in the parotid glands. ... it was possible to transfer PspX25's ability for high-level parotid gland expression to the Lama construct.

Laursen et al., "A cassette for high-level expression in the mouse salivary glands" *Gene* 198:367-372 (1997); and

> A novel Psp derived 9.7 kb parotid gland expression cassette, Lama IV, carrying all known regulatory regions in the PSP gene was expressed at high-levels in the parotid glands and should prove highly useful for expression of heterologous proteins in the saliva of transgenic mice.

Laursen et al., "The main regulatory region in the murine PSP gene is a parotid gland enhancer" *Transgenic Res.* 7:413-420 (1998). These teachings clearly indicate that the Applicants' specification is enabled for salivary gland protein expression because those having ordinary skill in the art would be aware of the proven state of the art for the Applicant's disclosed promoter expression systems.

A. The Specification Specifically Relates To Regulatory Sequences

The Examiner provides the following statement:

> ... the specification while suggesting that certain regulatory elements (from PSP and B1-Isp genes) could be used failed to disclose the actual nucleotide sequences of such elements ...

Office Action pg. 4. The Applicant disagrees and, for example, points to the following teaching when describing PSP regulatory control regions:

> The region of 5' flanking DNA required for salivary gland-specific expression is about 4.6 kb; but, longer regions, extending farther upstream may provide higher levels of expression.

Applicant's Specification pg 27 ln 15-18. Further, the Examiner discounts the Applicant's reliance on subject matter known in the art as "improper incorporation by reference" regarding Mikkelsen, Larson and Mirels at pages 27-28 of the specification:

> Applicant is reminded that subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication.

Office Action pg. 4. The Examiner is respectfully requested to reconsider the Applicant's argument presented in the previous response. It was clearly stated that these "incorporation by reference" statements are intended to "establish the state of the art". The Examiner has presented no evidence to rebut the Applicant's demonstration that the nucleotide sequences for several salivary gland promoters taught to successfully practice the Applicant's invention were known in the art. This intent by the Applicant is clearly stated in the specification:

> Promoters and other regulatory elements for making genetic and/or transgenic constructs that can be used to produce polypeptides and/or proteins in salivary gland cells and in saliva of transgenic mammals in accordance with the invention herein disclosed can be obtained by methods well known and readily available to those of skill in the cloning arts.

Applicant's Specification, pg. 34 ln 1-5. The Applicant has guided one having ordinary skill in the art to specific references having operable regulatory sequences. For the Examiner to make reference to an isolated remark in Samuleson regarding the "limitations" of known promoter sequences is not relevant as the Applicant points to specific promoters already known to be usable.

B. The Examples Provide Adequate Guidance To Create Transgenic Animals

The Examiner objects to the Examples within the specification because:

> ... the working examples failed to disclose which salvia regulatory elements were used in the creation of the transgenic cows.

Office Action pg. 5. The Applicant disagrees and argues that the provided examples are prophetic and draw support from the specification as discussed above and the arguments provided in the previous Office Action response (herein incorporated by reference). The Examiner is reminded that Examples are not required, much less "working examples".[2] The Examiner cites *Genentech v. Novo Nordisk* to support this rejection. The Examiner, however, has not fully considered the facts by which *Genentech* was decided.

Under *Genentech* the "starting materials" can be described in the specification, and are not limited to appearing in the actual Examples. The Applicant's instant specification provides many, many publications that are incorporated by reference to show the "state of the art" (*supra*). This was not the case in *Genentech*:

> Essentially, Genentech's argument is that the knowledge of one skilled in the art was sufficient to provide all the missing information ... and to the specification's explicit reference to British Patent 2008123-A.

Genentech v. Novo Nordisk, 208 F.3d 1361, 1365, 42 USPQ.2d 1001 (1997). In other words, *Genentech's* specification apparently had a single reference and a statement that everything else necessary to practice the invention was known to those having ordinary skill in the art. The Applicant has provided all references necessary to guide one having ordinary skill in the art to successfully make and use the claimed invention. Consequently, the Applicant believes that the Examiner's reliance on *Genentech* for 'lack of starting materials' is misplaced because the facts within *Genentech* are not consistent with the instant specification.

C. The Claims Convey Germline Transmission

The Examiner argues that the claims do not convey germline transmission because they can be:

> ... broadly interpreted to read on a single cell ... [that] ... would not result in a collectable amount of the polypeptide.

or,

[2] "... [i]t is well established that examples are not necessary . . . " *Ex parte Nardi and Simier,* 229 U.S.P.Q. 79, 80 (Bd. Pat. App. & Int'f. 1986).

> ... interpreted to read somatic cell gene transfer, wherein the cells of the salivary glands ... have been administered vectors .... result[ing] in both salivary specific and systemic polypeptide expression ...

Office Action pg. 6. The Applicant disagrees because the Examiner is clearly speculating. Claims 1 and 20 recite "a transgenic non-human mammal whose genome comprises", and Claim 41 recites "a transgenic bovine whose genome comprises". These terms cannot be interpreted as referring to "a single cell". Even if this interpretation is proper (which it is not), inoperable embodiments do not prevent patentability. It is well settled patent law that a claim may contain many inoperable elements (even though the Applicant believes this not to be the case here):

> ... the mere possibility of inclusion of inoperative . . . [subject matter] does not prevent allowance of broad claims ... many patented claims read on vast numbers of inoperative embodiments.

Application of Cook, 439 F.2d 730, 734, n4, 735169 U.S.P.Q. 298 (CCPA 1971), and

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude . . . possible inoperative substances. . . .'

Atlas Powder Co. v. E.I. Du Pont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409 (Fed. Cir. 1984). Consequently, even if the Examiner is correct that organisms comprising a single transgenic cell may not secrete detectable exogenous protein (which is highly speculative), this is not an appropriate basis on which to reject the present claimed embodiment. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicant has amended Claim 29 to recite "whose genome comprises" and added new Claim 50 to further define the embodiment wherein the genome may "comprise a plurality of cells". This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicant's business interests, better define one embodiment and expedite the prosecution of this application.

The Applicant respectfully requests the Examiner to withdraw the present rejection.

CONCLUSION

The Applicant believes that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect at 617.984.0616.

Dated: February 2, 2007

By: 

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1: Gene. 1997 Oct 1;198(1-2):367-72.

A cassette for high-level expression in the mouse salivary glands.

Laursen J, **Hjorth JP**.

Department of Molecular and Structural Biology, University of Aarhus, Denmark.

Expression in the mouse salivary glands may be used as a model system for studies involving oral cavity delivery of gene products. Previously, sequences from the mouse Psp gene were used to build a minigene construct denoted 'Lama'. This construct was used as a cassette for expression of human factor VIII light chain in mouse saliva. However, whereas the endogenous Psp mRNA is the most abundant protein-coding transcript in the parotid glands, the Lama mRNA was expressed below 1% of the level of Psp mRNA in these glands. Here, we show that a 25-kb cosmid-derived DNA fragment (PspX25) carrying the structural gene and large flanking areas of Psp is expressed in all 14 analysed lines in the parotid glands. The average level of transgene expression was estimated to be 45% of that of the endogenous Psp gene. More importantly, it was possible to transfer PspX25's ability for high-level parotid gland expression to the Lama construct.

PMID: 9370303 [PubMed - indexed for MEDLINE]

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1: Immunopharmacology. 1997 Jun;36(2-3):221-7.

Links

Expression of human tissue kallikrein in rat salivary glands and its secretion into circulation following adenovirus-mediated gene transfer.

Wang C, **Chao C**, **Chao L**, **Chao J**.

Department of Biochemistry and Molecular Biology, Medical University of South Carolina, Charleston 29425-2211, USA.

Replication-deficient adenovirus Ad.CMV-cHK, expressing human tissue kallikrein under the control of the cytomegalovirus enhancer/promoter, was introduced into rat salivary glands via a direct intracapsular injection. A single injection of Ad.CMV-cHK at a dose of 4 x 10(9) pfu resulted in a sustained expression of human tissue kallikrein in rat salivary glands. The level of immunoreactive human tissue kallikrein in rat sera was the highest at 1 day post gene delivery when both salivary glands were injected and decreased in a time-dependent manner after gene delivery. Human tissue kallikrein levels in sera increased concomitantly with the amount of adenovirus used in direct salivary injection. The detection of human tissue kallikrein in sera after gene delivery into salivary glands provided direct evidence indicating that rat salivary glands secrete locally synthesized human tissue kallikrein to the systemic circulation. The direct injection of salivary glands with replication-deficient adenovirus could provide a systemic route for gene delivery for studying salivary gland function and development. Targeted gene delivery to the salivary gland may provide the means to express therapeutic proteins in saliva and the systemic circulation.

PMID: 9228550 [PubMed - indexed for MEDLINE]

Related Links

Gene therapy in hypertension:

Kallikrein gene therapy: a new strategy for

Human kallikrein gene delivery attenuates

1: Transgenic Res. 1998 Nov;7(6):413-20.

The main regulatory region in the murine PSP gene is a parotid gland enhancer.

Laursen J, Krogh-Pedersen H, Dagnaes-Hansen F, Hjorth JP.

Department of Molecular and Structural Biology, University of Aarhus, Denmark.

The murine PSP gene is expressed at a high-level in the parotid glands. To extend the knowledge of parotid gland expression and develop tools for expression of heterologous proteins in this tissue, the regulation of the PSP gene was studied using transgenic mice. High-level parotid gland expression of the PSP gene was indicated to depend on a novel regulatory region situated between -8.0 and -6.5 kb. Together with previous results this indicates that the main regulatory elements in the PSP gene are situated between -8.0 to -3.1 kb. This region was shown to activate a heterologus SV40 early promoter in the parotid glands of transgenic mice, suggesting that the PSP gene is controlled by enhancer sequences. A novel Psp derived 9.7 kb parotid gland expression cassette, Lama IV, carrying all known regulatory regions in the PSP gene was expressed at high-levels in the parotid glands and should prove highly useful for expression of heterologous proteins in the saliva of transgenic mice.

PMID: 10341449 [PubMed - indexed for MEDLINE]